the racemate [(±)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one] forms part of the state of the art to applicants' invention. However, even accepting for purposes of this response that the claimed invention may infringe claims directed to the racemate, applicants' claims are still patentable. Non-infringement is not a standard for patentability.

35 U.S.C. § 101 specifically acknowledges the patentability of "any useful process, machine, manufacture, or composition of matter, and new and useful improvements thereof" [emphasis added]. Many new and useful improvements of patented processes, machines, or compositions of matter infringe patents directed to their older counterparts. Yet, this does not render the improvements unpatentable. Similarly, infringement is not a standard for anticipation or obviousness under 35 U.S.C. § 102 or § 103. Selection inventions may possess unexpected properties that are novel and unobvious even though they are encompassed by claims of an issued patent.

The Examiner has cited two cases to support the rejections under § 102 and § 103. Eli Lilly & Co. Inc. v. Generix Drug Sales Inc., 169 USPQ 13 (5th Cir. 1972) relates to the issue of patent infringement of claims directed to a racemic mixture by an enantiomerically enriched compound of the same formula. It does not address the issue of the patentability of the enantiomerically enriched compound over the racemic mixture. Accordingly, this case is not relevant to applicants' claims.

In re Adamson, 125 USPQ 233 (CCPA 1960), while more relevant, is clearly distinguishable from applicants' invention. In Adamson, the Court of Customs and Patent Appeals held that a laevo (-)-enantiomer of a substituted propanol with spasmolytic activity was not patentable over a reference disclosing a

racemic mixture of the same formula because the higher activity of the laevo enantiomer was not unexpected. Adamson's laevo-isomer was approximately twice as active and slightly more toxic than the racemate, while the dextro-isomer was virtually inactive as an antispasmodic.* The toxicity of the racemate was shown to lie between that of its isomers -- a fact which the court found to be particularly expected. In contrast, applicants' enantiomerically enriched compounds possess entirely unexpected and unobvious characteristics over the racemate. These unexpected properties render the claimed compounds patentable.

Patentability of compounds possessing unexpected activity over compounds with closely related structures has ample precedence in case law. For example, in In re Papesch, 137 USPQ 43, (CCPA 1963) the Court of Customs and Patent Appeals held that ethyl- and n-butyl-substituted heterocyclic compounds with unexpected anti-inflammatory activity were patentable over previously disclosed methyl-substituted compounds, because

> "[i]f that which appears, at first blush, to be obvious though new is shown by evidence *not* to be obvious, then the evidence prevails over surmise or unsupported contention and a rejection based on obviousness must fall" (emphasis in original). Id. at 48.

More recently, Court of Appeals for the Federal Circuit, interpreting the "Papesch doctrine" held that

> "evidence of unobvious or unexpected advantageous properties may rebut a *prima facie* case of obviousness based on structural similarities.... Such evidence may include data showing that a compound is unexpectedly superior in a property it shares with prior art compounds."

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* These results are self-consistent and expected if one considers that the racemate is a 1:1 mixture of laevo and dextro enantiomers. Thus, when only one enantiomer is active, the racemate should be 50% as active at the same concentration because only half of its constituents have activity. This is exactly what Adamson had observed.

In re Chupp, 2 USPQ2d 1437, 1439 (Fed.Cir. 1987).

The prior art does not teach the claimed compounds substantially free of the (+)-enantiomer. "Hence, there is no anticipation under § 102, because the exclusion of a claimed element from a prior art reference is enough to negate anticipation by that reference." Atlas Powder Co. v. E. I. du Pont de Nemours & Co., 224 USPQ 409, 411 (Fed.Cir. 1984). See also, Brenner v. Ladd, 147 USPQ 87, 91 (D.D.C. 1965)

> "... plaintiff's L-acl is not considered by this Court to be anticipated by the solution of DL-acl disclosed in Francis et al. even through [sic] a racemic compound such as DL-acl may dissociate in solution as disclosed by Karrer. A solution of L-acl contaminated by D-acl is not equivalent to a solution of pure L-acl ...."

Accordingly, applicants request that the Examiner withdraw the § 102 rejection.

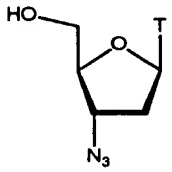
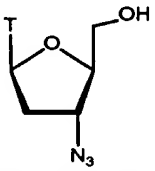
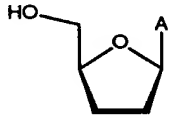
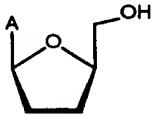
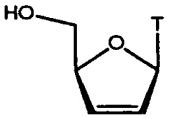
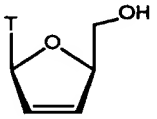
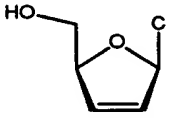
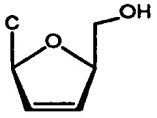
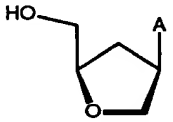
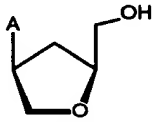
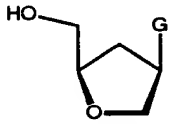
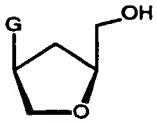
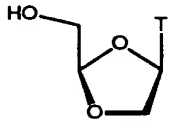
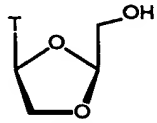
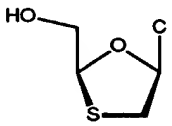
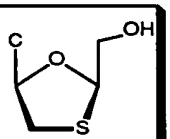
The claimed invention is also not obvious under 35 U.S.C. § 103. Applicants have provided evidence of the unexpected and superior properties of their enantiomerically enriched compounds over the known racemate. As applicants will demonstrate below, at the time the invention was made, those of ordinary skill in the art would have not expected the "non-natural" enantiomer of a nucleoside analogue to have any notable antiviral activity. Applicants' discovery that the "non-natural" enantiomer of cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one is a potent antiviral agent with extremely low toxicity was, therefore, surprising and unexpected.

The compounds of the present invention belong to the general class of compounds collectively known as antiviral nucleoside analogues. The antiviral activity of nucleoside analogues is believed to stem from their ability to disrupt the genetic propagation processes in viruses. By mimicking the

natural nucleosides that participate in these processes, antiviral nucleoside analogues (or any of their metabolic derivatives) may competitively inhibit enzymes that act upon nucleosides, or incorporate non-productively into any of the nucleic acid components of the viral life cycle.

As the search for ever more effective antiviral agents has continued, scientists have prepared and tested many of the known nucleoside analogues in enantiomerically pure form. Prior to applicants' invention, experimental results and comparative tests on the activity of enantiomer pairs of nucleoside analogues had suggested that the useful antiviral activity resides mainly or exclusively in the enantiomer having the pseudo-"natural" configuration at its chiral centers (see Table I). For example, the "natural" enantiomers of azidothymidine (AZT), dideoxyadenosine (ddA), dideoxydidehydrothymidine (d4T), and dideoxydidehydrocytosine (d4C), all show potent activity against HIV, whereas the "nonnatural" enantiomers are either inactive or have significantly diminished anti-HIV activity (Table I, entries 1-4). Similarly, the so-called "iso" nucleoside analogues -- wherein the oxygen atom occupies a different position in the sugar ring of the nucleoside analogue than it does in natural nucleosides -- appear to be active only when their absolute configuration corresponds to the absolute configuration of "natural" nucleosides (Table I, entries 5 and 6). This trend is also observed in 1,3-dioxolane nucleoside analogues -- wherein the 3' carbon of the sugar base has been replaced by an oxygen atom (Table I, entry 7). Here again, the antiviral activity was found to reside mainly in the enantiomer having the "natural" absolute configuration.

TABLE I. Antiviral activity of some nucleoside analogues and their enantiomers.

Entry	Name	"Natural"	"Nonnatural"
1	Azidothymidine (AZT)	 ACTIVE	 <10,000 times active
2	Dideoxyadenosine (ddA)	 ACTIVE	 INACTIVE
3	Dideoxydidehydrothymidine (d_4T)	 ACTIVE	 INACTIVE
4	Dideoxydidehydrocytosine (d_4C)	 ACTIVE	 INACTIVE
5	Iso-dideoxyadenosine (iso-ddA)	 ACTIVE	 INACTIVE
6	Iso-dideoxyguanosine (iso-ddG)	 ACTIVE	 INACTIVE
7	3'-oxo-2',3'-dideoxythymidine (dioxolane-T)	 ACTIVE	 substantially reduced activity
8	3'-thia-2',3'-dideoxycytosine (BCH-189)	 ACTIVE	 **ACTIVE!**

These results also conform to the generally accepted "molecular mimicry" mechanism of action of antiviral nucleoside analogues. The skilled artisan would expect nucleoside analogues having the "natural" stereochemical configuration to possess greater biological activity because they are better molecular mimics of natural nucleosides than their "non-natural" enantiomers. As a corollary, one of skill in the art would reasonably expect the "non-natural" enantiomer to have very little or altogether abolished activity.

Applying this knowledge -- i.e. the trend established in known enantiomeric pairs of antiviral nucleoside analogues, and the generally accepted mechanism of action of these compounds -- to the known racemic 1,3-oxathiolane nucleoside analogues, the skilled artisan would, therefore, expect the claimed "unnatural" enantiomer of a 1,3-oxathiolane to have little or no antiviral activity. Applicants' invention is, surprisingly, contrary to this expectation (Table I, entry 8).

Applicants disclose the activity of their claimed compounds at pages 27-28, and Tables 1 and 2 of the specification. Tables 1 and 2 demonstrate that the "nonnatural" enantiomer is equal to or better than the "natural" (+)-enantiomer both in inhibition of HIV-infected cell syncytium formation and in blocking of HIV p24 (glycoprotein) synthesis in a variety of virally infected cell lines. These results are completely unexpected and unobvious because for the first time in the long pharmacological history of nucleoside analogues, (1) the "non-natural" enantiomer has shown a high level of biological activity, (2) the antiviral activity does not reside predominantly with a single enantiomer, but rather is almost evenly distributed between the two, and (3) the toxicity resides predominantly in the natural enantiomer and is much lower in the

"non-natural" enantiomer thereby providing a higher therapeutic index.

The scientific community has also attested to the unexpectedness of this discovery. For example, the enantiomeric forms of the 1,3-oxathiolanes of the present invention have been independently studied by Beach et al., "Synthesis Of Enantiomerically Pure (2'R,5'S)-(-)-1-[2-(Hydroxymethyl) oxathiolan-5-yl]cytosine As A Potent Antiviral Agent Against Hepatitis B Virus (HBV) And Human Immunodeficiency Virus (HIV)", J. Org. Chem., 57, pp. 2217-2219 (1992) (copy enclosed). Beach notes that "the ß-D-isomer of nucleosides are in general the biologically active isomers" (page 2217, column 1) but concludes that "(2'R,5'S)-(-)-BCH-189 **3** [is] more potent than (2'S,5'R)-(+)-BCH-189 **2** by at least one order of magnitude. The significance of this finding is the fact that this is the first example of an L-like nucleoside found to be more potent than a D-like nucleoside" (page 2219, column 2).

Similarly, Chang et al., "Deoxycytidine Deaminase-Resistant Stereoisomer Is The Active Form Of (±)-2',3'-Dideoxy-3'-Thiacytidine In The Inhibition Of Hepatitis B Virus Replication", J. Biol. Chem., 276, pp. 13938-13942 (1992) (copy enclosed) independently studied antiviral activities of the enantiomerically enriched 1,3-oxathiolane nucleoside analogues of this invention. Chang acknowledges that "[i]t has always been assumed that the active stereoisomer of these analogs would be the one which most closely mimicked the natural nucleoside" (page 13941, column 2). Chang also confirms that "[t]his is the first nucleoside analog with the unnatural sugar configuration demonstrated to have antiviral activity" (abstract, page 13938).

See also, the independent report of R. F. Schinazi et al., "Activities Of The Four Optical Isomers Of 2',3'-

Dideoxy-3'-Thiacytidine (BCH-189) Against Human Immunodeficiency Virus Type 1 In Human Lymphocytes", Antimicrobial Agents And Chemotherapy, 36(3), pp. 672-676 (1992) (copy enclosed) -- "[t]he unexpected finding that certain L isomers of nucleoside analogs of BCH-189 are potent and selective antiviral agents opens new approaches for the treatment of viral infections with nucleosides with the unusual L conformation [sic]."

Applicants' discovery has provided the world with a considerably less toxic and superior antiviral agent compared with other known antiviral nucleoside analogues, including the racemic 1,3-oxathiolanes. The lower toxicity of the (-)-enantiomer is documented at page 29, Table 3, of the specification. Table 3 demonstrates that the claimed (-)-enantiomer is up to 100 times less toxic than the (+)-enantiomer and up to 30 times less toxic than the corresponding racemate. This implies that the "non-natural" enantiomers of this invention are not only unexpectedly active, but surprisingly nontoxic for an antivirally active compound. Accordingly, applicants request that the Examiner withdraw the rejection under 35 U.S.C. § 103.

The Examiner has rejected claims 19 and 20 under 35 U.S.C. § 112, first and second paragraphs. Specifically, the Examiner contends that "[o]ne has no way of knowing what 'pharmaceutically acceptable derivative thereof' applicants have in mind". Applicants disagree.

Applicants define the term "pharmaceutically acceptable derivatives" in full, clear, concise and exact terms at page 2, lines 31-46 of the specification as:

(1) salts of compound (A);

(2) esters of compound (A);

(3) salts of esters of compound (A); and

(4) compounds which provide -- either directly or indirectly -- compound (A) or an antivirally active metabolite or residue thereof when administered to a recipient.

The specification also provides a detailed description of how the compound (A) may be modified to provide pharmaceutically acceptable derivatives (page 2, line 39 to page 3, line 44) and of the preferred pharmaceutically acceptable derivatives of this invention (page 2, line 51 to page 3, line 10). Upon reading the specification, a person of ordinary skill in the art could easily make and use the described pharmaceutically acceptable derivatives using conventional synthetic methodology.

Finally, the term "pharmaceutically acceptable derivative" is typically accepted by the United States Patent and Trademark Office in patents claiming pharmaceutically useful compounds. See, e.g., claim 1 in each of United States patents 4,868,306; 4,885,31; 4,491,357; 4,914,126; 4,920,196; 4,950,477; 5,100,647; 5,013,760; and 5,019,591 (copies enclosed). Accordingly, in view of the support provided in the specification and wide acceptance of the term in the art, applicants request that the Examiner withdraw the rejection.

The Examiner has reminded applicants of their obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made. Applicants confirm that the subject matter of all of the pending claims was commonly owned at the time the inventions covered therein were made.

Applicants note that the Examiner has not returned an initialized copy of PTO form 1449, submitted by applicants on September 18, 1992. Applicants have attached a copy of the